Immunomodulators, Atopic Dermatitis
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
pimecrolimus (Elidel®)[1]	Valeant	Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate Atopic dermatitis (AD) in non-immunocompromised patients 2 years of age and older who have failed to respond to other topical prescription drugs or when those treatments are not advisable
tacrolimus (Protopic®)[2]	generic	Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe AD in non-immunocompromised patients 2 years of age and older who have failed to respond to other topical prescription drugs or when those treatments are not advisable ▪ 0.03% ointment approved for patients 2 years to 15 years old ▪ 0.03% ointment and 0.1% ointment approved for adults

OVERVIEW[3,4,5,6,7,8,9,10]

Atopic dermatitis (AD) is a chronic, non-contagious, inflammatory disease of the skin resulting from a combination of genetic and environmental factors. Approximately 70% of patients diagnosed with AD have a positive family history of atopic diseases. The odds of developing AD are two to three times higher in children with one atopic parent and increase to three to fives times higher if both parents are atopic.

Often referred to as "eczema," AD affects about 17.8 million Americans and accounts for 10 to 20% of all visits to the dermatologist. The majority of patients have a "mild" form of the disease, meaning the AD affects less than 20% of the body surface area. Still, left untreated, even the mild form can result in itching and rashes that becomes a significant and visible reminder of the disease. For people whose AD affects more than 20% of their bodies, the disease can be a physically painful condition.

Although symptoms of AD can develop at any age, it has been estimated that 60% of patients develop symptoms in the first year of life, while 90% develop symptoms before the age of five. The majority of affected patients have resolution of the disease by adulthood, 10 to 30% do not, and a smaller percentage first develops symptoms as adults. Onset after age 30 is less common and is often caused by exposure of the skin to harsh or wet conditions. AD commonly occurs in patients affected by asthma and other allergic conditions and is associated with elevated serum IgE levels. People who reside in cities and in dry climates appear to be more likely to develop this condition.

AD is characterized by extremely dry, itchy skin on the insides of the elbows, behind the knees, and on the face, hands, and feet. In response to the intense itching, patients may scratch or rub the affected area, which leads to further irritation and inflammation. As the skin loses moisture from the epidermal layer, it becomes increasingly dry and may begin to crack, weep, crust, and scale. This damage to the integrity of the skin renders it less protective and more prone to infection. Despite the chronic nature of this dermatologic condition, there may be periods of the disease when the skin improves and periods when the skin worsens. Irritants, such as detergents, fumes, tobacco smoke, and alcohol-containing skin products, and allergens like dust mites, pollen, and animal dander can exacerbate AD or cause "flare ups."

Both the Joint Council of Allergy, Asthma and Immunology and the American Academy of Dermatology (AAD)/American Academy of Dermatology Association guidelines from 2014 state that topical corticosteroids and emollients are the standard of care for the treatment of AD.[11] Patients with this disease are prone to *Staphylococcus aureus* infections, and treatment with oral or topical antibiotics may be useful. Topical immunomodulating agents are effective in the treatment of AD. For severe AD, oral immunomodulating agents may be needed. In December 2007, the National Institute for Health and Clinical Excellence (NICE) published clinical guidelines on the diagnosis, evaluation, and management of atopic eczema in children ≤12 years of age.[12] The NICE guidelines promote a stepwise approach, based on severity of AD, for management with regular emollients and intermittent topical corticosteroids forming the basis of treatment. For patients whose eczema is not controlled by topical corticosteroids, or when there is a serious risk of adverse events from topical corticosteroids, topical calcineurin inhibitors, tacrolimus or pimecrolimus, are used as second-line treatments.

Although topical corticosteroids are the standard of care in the treatment of AD, dermatologic effects, such as striae, atrophy, and tachyphylaxis, as well as potential non-dermatologic effects on linear growth rate, bone density, and hypothalamic-pituitary-adrenal (HPA) axis suppression, limit the long-term use of these agents.

Pimecrolimus (Elidel) and tacrolimus (Protopic) are calcineurin inhibitors that act locally on T-cells by suppressing cytokine transcription. Inhibiting cytokine production leads to decreased inflammation and also serves to block T-cell activation which can trigger and maintain skin inflammation. These immunomodulating agents have been shown to reduce the extent, severity, and symptoms of AD in adults and children.

The Food and Drug Administration (FDA) in 2006 issued a public health advisory to inform health care professionals and patients about the potential cancer risk associated with use of pimecrolimus (Elidel) and tacrolimus (Protopic).[13] Animal studies, case reports in a small number of patients, and knowledge of the mechanism of action of these drugs form the basis for concern. Based on the advice of the FDA Pediatric Advisory Committee, the FDA required labeling changes for pimecrolimus and tacrolimus, including placement of a black box warning to the health care professional and a Medication Guide to be distributed by pharmacists to patients with each new and refill prescription. Human studies that definitively link these drugs to cancer could take ten years or longer to complete. With the true risk unknown, the FDA advises that these agents be used as second-line treatment options only as labeled for the short-term and intermittent treatment of AD after other prescription treatments have failed or cannot be tolerated.

PHARMACOLOGY[14,15,16]

Pimecrolimus (Elidel) is a derivative of the macrolactam ascomycin. It binds to the intracellular protein macrophilin-12 (FKBP-12) and inhibits the calcium-dependent phosphatase calcineurin. As a consequence, it inhibits T-cell activation by blocking the transcription of cytokines. Cytokines of both the Th1-type (IL-2 and interferon-gamma) and Th2-type (IL-4 and IL-10) are inhibited in T-cells. In addition, pimecrolimus prevents the release of inflammatory cytokines and mediators from mast cells after stimulation by antigen/IgE. Pimecrolimus has no effect on the growth of fibroblasts or keratinocytes.

Tacrolimus (Protopic) is a topical macrolactam agent. It exerts its pharmacologic activity by binding to FKBP-12. A complex is then formed which includes calcineurin. This complex prevents the phosphatase activity of calcineurin and thus prevents gene transcription for the formation of various lymphokines (IL-2, interferon-gamma). Other genes that may also be inhibited include those for the formation of IL-3, IL-4, IL-5, granulocyte macrophage colony stimulating factor, and tumor necrosis factor-alpha.

PHARMACOKINETICS[17,18]

Minimal systemic absorption occurs from topical use of pimecrolimus (Elidel) or tacrolimus (Protopic).

In adults treated with pimecrolimus for AD (body surface area [BSA] involvement 13 to 62%) for up to a year, systemic concentrations were non-detectable (> 0.5 ng/mL) in the majority of patients. In patients with detectable concentrations of pimecrolimus, no accumulation was noted, and concentrations were routinely less than 1.5 ng/mL.

The systemic exposure to pimecrolimus 1% cream administered twice daily for three weeks was studied in 28 pediatric patients (age range eight months to 14 years and BSA involvement 20 to 80%). Blood concentrations of pimecrolimus were <2 ng/mL with 60% (96/161) of the blood samples having blood concentration below the limit of quantification (0.5 ng/mL). In another pediatric trial (patient age three to 23 months and BSA involvement ten to 92%), the highest blood concentration noted was 2.6 ng/mL. Pimecrolimus use is not recommended in pediatric patients younger than 24 months.

The systemic concentration of tacrolimus 0.1% ointment was studied after single and multiple topical dosing in three pharmacokinetic studies with 88 adult patients. The pooled results indicate that tacrolimus is minimally absorbed after the topical application. The systemic concentration ranged from undetectable to 20 ng/mL and, in 78 of 88 patients, the peak concentration was less than 2 ng/mL. In general, as treatment continued, systemic exposure declined as the skin returned to normal.

After topical administration of tacrolimus 0.1% ointment, the peak concentration reported in 20 pediatric patients, ages six to 13 years, was less than 1.6 ng/mL.

In a pharmacokinetic study of 14 pediatric patients with AD, between the ages of two to five years, peak blood concentrations of tacrolimus ranged from undetectable to 14.8 ng/mL after single or multiple doses of tacrolimus 0.03% tacrolimus ointment, with 86% of patients having peak blood concentrations below 2 ng/mL throughout the study.

CONTRAINDICATIONS/WARNINGS[19,20,21]

Both products in this class have a black box warning regarding the long-term safety of topical calcineurin inhibitors, which has not been established. Rare cases of malignancy have occurred. Avoid continuous long-term use of calcineurin inhibitors and limit application to areas affected by AD.

The safety of these drugs has not been established beyond one year of non-continuous use.

PRECAUTIONS[22,23]

Bacterial and viral infections of treatment sites must be resolved prior to AD treatment.

AD patients should avoid use on malignant or pre-malignant skin conditions. In addition, some malignant skin conditions, such as cutaneous T-cell lymphoma (CTCL), may mimic atopic dermatitis.

Patients with Netherton's syndrome or other skin diseases that may allow for increased systemic absorption should not use these products.

Increased risk of varicella zoster virus infection, herpes simplex virus infection, and eczema herpeticum is associated with use of products from this class.

Patients with AD should minimize or avoid natural and artificial sunlight, even if the product is not present on the skin. It is not known whether topical pimecrolimus and tacrolimus therapy interferes with skin response to ultraviolet damage.

If signs and symptoms of AD do not resolve within six weeks, patients should have their physician re-examine and confirm the diagnosis.

Patients who develop lymphadenopathy should have the etiology examined to determine its cause. In clinical studies, less than 1% of cases of lymphadenopathy were reported while using pimecrolimus and tacrolimus, and noted to resolve upon appropriate antibiotic therapy. The majority of these cases had either a clear etiology or resolved. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, pimecrolimus or tacrolimus should be discontinued.

Safety of these products under occlusive dressings, which may promote systemic exposure, has not been studied and therefore should not be used by patients.

DRUG INTERACTIONS[24,25]

Potential interactions between these agents and other drugs, including immunizations, have not been evaluated. Due to low blood levels of pimecrolimus and tacrolimus detected after topical application, systemic drug interactions are not expected. However, concomitant administration of known CYP 3A4 inhibitors (erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers, and cimetidine) with pimecrolimus (Elidel) or tacrolimus (Protopic) in patients with widespread and/or erythrodermic disease should be done with caution.

ADVERSE EFFECTS

Drug	Skin Burning (%)	Pruritus (%)	Skin Erythema (%)	Rash (%)
pimecrolimus 1% (Elidel)[26] n=328 adults	25.9	5.5	2.1	0
pimecrolimus 1% (Elidel) n=272 children	8.5	1.8	2.2	4 (viral rash in infants)
vehicle (pimecrolimus studies) n=75 children	6.7	0	0	0
tacrolimus 0.1% (Protopic)[27] n=209 adults	58	46	28	2
tacrolimus 0.03% (Protopic) n=210 adults	46	46	25	5
vehicle (tacrolimus studies) n=212 adults	26	37	20	1
tacrolimus 0.03% (Protopic) n=118 children	43	41	12	2
vehicle (tacrolimus studies) n=116 children	29	27	13	4

Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive.

SPECIAL POPULATIONS[28,29]

Pediatrics

Agents in this category are not approved for use in patients less than two years of age.

Clinical trials with pediatric patients are included in the Clinical Trials section.

Pregnancy

Both agents are Pregnancy Category C.

Renal Impairment

Although the effect of renal insufficiency on the pharmacokinetics of agents in this class has not been evaluated, no dose adjustment is recommended.

Hepatic Impairment

Although the effect of hepatic impairment on the pharmacokinetics of agents in this class has not been evaluated, no dose adjustment is recommended.

Immunocompromised

Neither product should be used in adult and pediatric patients who are immunocompromised.

DOSAGE AND ADMINISTRATION

Drug	Adult	Children (2-15 yrs)	Availability
pimecrolimus 1% (Elidel)[30]	Apply a thin layer to affected skin twice daily	Apply a thin layer to affected skin twice daily	30, 60, 100 gm tubes of cream
tacrolimus 0.03% (Protopic)[31]	Apply a thin layer to affected skin twice daily	Apply a thin layer to affected skin twice daily	30, 60, 100 gm tubes of ointment
tacrolimus 0.1% (Protopic)	Apply a thin layer to affected skin twice daily	--	30, 60, 100 gm tubes of ointment

Pimecrolimus (Elidel) cream and tacrolimus (Protopic) ointment are not associated with skin atrophy and, therefore, can be used on sensitive areas such as the face, neck, and skin folds.[32,33]

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Comparative studies that are investigator-blinded have not been included.[34,35,36]

Adults

pimecrolimus (Elidel) versus topical corticosteroids

A randomized, double-blind, multicenter European study compared the long-term safety and tolerability of pimecrolimus 1% cream and topical corticosteroids (TCS) in 658 adults with moderate-severe AD.[37] Patients applied either pimecrolimus or TCS (e.g., triamcinolone acetonide 0.1% cream and/or hydrocortisone acetate 1% cream) twice daily to all affected areas until complete clearance or for up to one year. A majority of patients treated with either pimecrolimus or TCS used the drug on a continuous basis over one year. In patients who had greater than 30% BSA involvement, the incidence rate of all skin infections was significantly lower in the pimecrolimus group than in the TCS group (95% confidence interval [CI] of the treatment difference: -25.3% to -3.4%). The most frequent application site reaction was burning (25.9% pimecrolimus and 10.9% TCS). Three TCS-treated patients reported skin striae. Efficacy was better in patients on continuous TCS therapy, although patients completing the study were similarly well-controlled in both groups. About 42% of the pimecrolimus-treated patients were maintained for one year without TCS.

tacrolimus (Protopic) versus topical corticosteroids

A randomized, double-blind study compared the efficacy and safety of twice daily tacrolimus ointment 0.1% to a corticosteroid ointment regimen in 972 adults with moderate to severe AD, for a maximum of six months.[38] Tacrolimus ointment was applied to all affected areas over the whole body. For the corticosteroid group, hydrocortisone butyrate ointment 0.1% was applied to affected areas on the trunk and extremities, and hydrocortisone acetate ointment 1% was applied to affected areas on the face and neck. The study primary endpoint was the response rate defined as the proportion of patients with at least 60% improvement in the modified Eczema Area and Severity Index (mEASI) between baseline and month three. More patients in the tacrolimus group responded to treatment by the third month compared to the corticosteroid group, 72.6% versus 52.3%, respectively ($p<0.001$). The tacrolimus patients also showed greater improvement in mEASI, EASI, affected body surface area, and physician and patient assessments of global response. More patients in the tacrolimus group experienced skin burning compared to the corticosteroid group, 52.4% versus 13.8%, respectively ($p<0.001$). Skin burning was mild to moderate in severity and decreased rapidly after the first week of treatment in the majority of patients. There was no increase in the incidence of infections or malignancies over time in either treatment group.

A three-week randomized, double-blind, parallel-group, multicenter study compared twice daily tacrolimus 0.03% and 0.1% ointment with hydrocortisone 17-butyrate 0.1% ointment in the treatment of 570 adults with moderate to severe AD.[39] Patients applied ointment twice daily to all affected areas for three weeks. The primary outcome of median modified eczema area and severity index (mEASI) mean area under the curve as a percentage of baseline was 47%, 36.5%, and 36.1% for patients who received 0.03% tacrolimus, 0.1% tacrolimus, and 0.1% hydrocortisone butyrate, respectively. There was no statistically significant difference between 0.1% tacrolimus and 0.1% hydrocortisone butyrate. The lower improvement in mEASI for 0.03% tacrolimus was statistically significant when compared with 0.1% tacrolimus ($p<0.001$) or hydrocortisone butyrate ($p=0.002$). The tacrolimus groups had more skin burning and pruritus at the application site compared to the hydrocortisone butyrate group ($p<0.05$).

Pediatrics

pimecrolimus (Elidel)

A double-blind, randomized study assessed the time of onset of pruritus improvement in 174 children and adolescents (aged two to 17 years) with mild to moderate AD with moderate to severe pruritus.[40] In the eight-day study, patients applied twice daily pimecrolimus 1% cream or vehicle control. Pruritus was assessed by subjects using a four-point pruritus severity scale (0-3). The primary outcome parameter, the time to a 1-point or more improvement from baseline for the pruritus score, was 48 hours in the pimecrolimus group and 72 hours for the vehicle group ($p=0.038$). From day three onward, significantly more patients receiving pimecrolimus had complete pruritus resolution compared to those receiving vehicle ($p=0.023$). At the end of the seven-day treatment, significantly more patients in the pimecrolimus group had improved or completed resolution of pruritus compared to the group assigned to the vehicle control ($p=0.008$).

A randomized, double-blind, multicenter study compared twice daily pimecrolimus cream 1% to vehicle cream in 521 patients aged two to 17 years, with a history of mild or moderate AD.[41] These patients were clear or almost clear of disease prior to randomization. Treatment was initiated at the first signs and/or symptoms of recurring AD. A moderately potent topical corticosteroid was allowed in both groups if, despite the application of study medication for at least three days, AD worsened (as confirmed by the investigator). The primary efficacy endpoint was the number of days on study without topical corticosteroid use for a flare. The mean number of topical corticosteroid-free days was significantly higher ($p<0.0001$) in the pimecrolimus group compared to the vehicle group (160.2 versus 137.7 days, respectively). Patients treated with pimecrolimus cream 1% experienced 50% fewer flares requiring topical corticosteroids than patients who received vehicle cream (mean number of flares 0.84 versus 1.68, respectively, $p<0.0001$).

A randomized, double-blind study of less than or equal to six weeks, followed by a six-week, open-label phase compared pimecrolimus cream 1% to vehicle twice daily in 200 children aged two to 11 years with mild to moderate facial AD dependent on or intolerant of topical corticosteroids.[42] Patients were treated with the pimecrolimus cream or vehicle twice daily until clearance of facial AD or for a maximum of six weeks. Significantly more patients on pimecrolimus compared to vehicle patients were cleared/almost cleared of facial AD (Investigators' Global Assessment 0/1) on day 22 (57.1% versus 36.0%, $p=0.004$) and day 43 (74.5% versus 51%, $p<0.001$). Median time to clearance was 22 days compared to 43 days for the pimecrolimus group versus the vehicle group, respectively. Statistically significant differences for pimecrolimus compared with vehicle were also seen on head and neck EASI, overall EASI, and head and neck pruritus scores. There were no differences in adverse events between treatment groups.

tacrolimus (Protopic)

A 12-month, randomized, multicenter study investigated whether twice-weekly tacrolimus 0.03% ointment can keep AD in remission and reduce the incidence of disease exacerbation in children.[43] In the initial open-label period, 267 children with AD applied tacrolimus 0.03% ointment twice daily for up to six weeks to all affected areas. When an Investigator Global Assessment (IGA) score of ≤ 2 was achieved, 250 patients entered the disease control period (DCP) and were randomized to receive tacrolimus or vehicle ointment twice weekly for 12 months. Exacerbations were treated with tacrolimus 0.03% ointment twice daily until an IGA ≤ 2 was regained; then randomized treatment was reinitiated. Proactive application of tacrolimus 0.03% ointment significantly reduced the primary outcome which was the number of disease exacerbations during the DCP that required substantial therapeutic intervention (median difference: 1.0; $p<0.001$; Wilcoxon rank-sum test), the percentage of disease exacerbation treatment days (median difference: 6.2; $p<0.001$; Wilcoxon rank-sum test), and increased the time to first disease exacerbation requiring intervention (median: 173 versus 38 days; $p<0.001$; stratified log-rank test). There were no differences in adverse events between treatment groups.

The safety and efficacy of tacrolimus 0.03% and 0.1% ointment for the treatment of AD were evaluated in a 12-week, randomized, double-blind, vehicle-controlled study of 351 children two to 15 years of age with moderate to severe AD.[44] The mean percentage of BSA affected was 47.7%. Significantly more patients ($p<0.001$) achieved clinical improvement of 90% or better with tacrolimus 0.03% or 0.1% ointment compared with vehicle. Significant improvements in the signs and symptoms of AD, percent BSA affected, and the patient's/caregiver's assessment of pruritus were also observed early in treatment and were maintained throughout the study. Adverse events with a statistically significantly

greater incidence in the tacrolimus 0.03% ointment treatment group compared with vehicle were limited to the sensation of skin burning, pruritus, varicella, and vesiculobullous rash ("blisters"). No adverse event occurred at a statistically higher incidence in the tacrolimus 0.1% ointment-treated group compared with vehicle. Both tacrolimus ointment concentrations were safe and significantly more effective than vehicle for the treatment of AD in children.

In the randomized, double-blind, vehicle-controlled multicenter trial, children ages seven to 16 years were treated with tacrolimus 0.03%, 0.1%, or 0.3% ointment twice daily or vehicle for up to 22 days with a two-week follow-up period.[45] The Physician's Global Evaluation of clinical response showed that 69% of patients in the 0.03% tacrolimus group, 67% in the 0.1% tacrolimus group, and 70% in the 0.3% tacrolimus group, compared with 38% in the vehicle group, had a marked to excellent (>75%) improvement or clearing of their AD (p=0.005, p=0.007, and p=0.004, respectively, for the three tacrolimus groups compared with the vehicle group). The mean percent improvement for the modified EASI at end of treatment for each of the tacrolimus groups (0.03%, 72%; 0.1%, 77%: and 0.3%, 81%) was significantly greater than that of the vehicle group (26%, p<0.001). The median percentage reduction in pruritus was significantly greater for tacrolimus-treated patients (74 to 89%) than for vehicle-treated patients (51%, p=0.027).

pimecrolimus (Elidel) versus hydrocortisone

In the one-year, controlled, double-blind study, 713 AD patients ages two to 17 years were randomized 2:1 to a pimecrolimus-based or conventional AD regimen consisting of vehicle and topical corticosteroids.[46] The proportion of patients who completed six or 12 months with no flares was approximately twice as high in the pimecrolimus group compared with control (61% versus 34.2% at six months; 50.8% versus 28.3% at 12 months). Fewer flares were observed in the pimecrolimus group regardless of baseline disease severity. There were no appreciable differences between treatment groups in the overall incidence of adverse events. The authors concluded that pimecrolimus ointment appears to be safe and effective in children with atopic dermatitis.

tacrolimus (Protopic) versus hydrocortisone

The efficacy and safety of tacrolimus 0.03% ointment applied once or twice daily over a three-week period were compared with the twice daily application of hydrocortisone acetate 1% ointment in children with moderate to severe AD.[47] The primary study endpoint was the percentage change in the modified EASI between baseline and treatment end. Patients ages two years to 15 years were randomized in the double-blinded study to tacrolimus 0.03% ointment once daily (n=207) or twice daily (n=210) or hydrocortisone acetate 1% twice daily (n=207). By the end of treatment, application of tacrolimus 0.03% ointment both once or twice daily resulted in significantly greater median percentage decreases in modified EASI (66.7 and 76.7%, respectively) compared with hydrocortisone acetate 1% (47.6%; p<0.001). Furthermore, the median percentage decrease in modified EASI was significantly greater for patients applying 0.03% tacrolimus twice daily compared with once daily (p=0.007). Patients with severe AD benefited especially from twice daily application of 0.03% tacrolimus ointment compared with once daily application (p=0.001). Transient mild to moderate skin burning occurred significantly more often in the tacrolimus groups but resolved in most cases within three to four days (p=0.028).

tacrolimus (Protopic) versus fluticasone

A randomized, double-blind, non-inferiority trial compared tacrolimus 0.03% ointment to fluticasone 0.005% ointment in 479 children ages two to 15 years old with moderate to severe AD who had not responded sufficiently to conventional therapies.[48] Ointments were applied twice daily until clearance or for a maximum of three weeks and, if lesions remained, once daily for up to three weeks further. Primary endpoint was week three response rate (improvement of ≥ 60% in modified Eczema Area and Severity Index and not withdrawn for lack of efficacy). Response rates were 86.3% and 91.5% with tacrolimus and fluticasone, respectively. Lower limit of the 95% CI was -11.8%; this exceeded the non-inferiority limit of -15% and met the primary endpoint. Moderate or better improvement on secondary endpoints of the physicians' global assessment occurred in 93.6% and 92.4% of patients in the tacrolimus and fluticasone groups, respectively, while median pruritus scores improved by 84% and 91.5%, respectively. Sleep quality improved by approximately 92% in both treatment groups. After day 21, new flare-up occurred in 5.5% and 11.3% of patients receiving tacrolimus and fluticasone, respectively. Mean times to new flares were 6.5 +/- 5 days and 8.6 +/- 5.2 days. Adverse events were similar between the two arms, but burning at application-site was higher in the tacrolimus arm.

META-ANALYSIS

A meta-analysis to evaluate the efficacy and safety of pimecrolimus cream 0.1% in the treatment of AD in the pediatric population was conducted up to July 2013.[49] The analysis included seven studies with a total of 2,170 pediatric patients and concluded that pimecrolimus cream 0.1% was not significantly better than the vehicle for AD based on the Odds Ratios (ORs). The ORs for response for pimecrolimus verses vehicle at day eight, day 26, and six weeks were (4.95, 95% CI, 2.79-8.80), (9.69, 95% CI, 4.12-22.83), and (3.83, 95% CI, 1.94-7.56), respectively. Pimecrolimus also did not show beneficial effects when analyzed for mild or absent pruritus at day four (OR 8.29, 95% CI, 3.88-17.72 favoring vehicle), day 43 (OR 1.81, 95% CI, 1.13-2.89 favoring vehicle), and one week (OR 2.29, 95% CI, 1.45 to 3.60 favoring vehicle) as compared with vehicle. There was no significant difference in achieving mild or absent pruritus in one study that compared pimecrolimus with tacrolimus (OR 0.94, 95% CI, 0.44-1.99). The care givers of the pediatric patients assessed that more patients showed an improvement in overall disease in the vehicle group at day eight (OR 3.3, 95% CI, 2.03-5.35), day 29 (OR 14.14, 95% CI, 6.87-29.13), and day 43 (OR 4.11, 95% CI, 2.59-6.52), as compared with pimecrolimus 0.1% group. There was no significant difference seen between the adverse effects in both groups (pimecrolimus versus vehicle/tacrolimus) (OR 1.19, 95% CI, 0.85, 1.65).

A meta-analysis conducted in 2005 concluded that success rates for tacrolimus (Protopic) and pimecrolimus (Elidel) were statistically similar.[50] A 2007 Cochrane Database systematic review found pimecrolimus was less effective than tacrolimus and also less effective than moderate to potent corticosteroids.[51] However, these results were based on mostly investigator-blinded trials.[52,53] Pimecrolimus was associated with significantly more overall withdrawals and skin burning compared to corticosteroids. There were more withdrawals with pimecrolimus than tacrolimus but no significant difference in proportions of patients experiencing adverse events.

A 2009 systematic review and meta-analysis found pimecrolimus was less effective than topical corticosteroids, but it showed that use of pimecrolimus for six months resulted in reduction in flares and had a steroid-sparing effect when used early in treatment.[54] Both 0.1% and 0.03% tacrolimus ointments were as effective as moderate potency corticosteroids and more effective than mild corticosteroids. Large, double-blind, comparative trials of pimecrolimus and tacrolimus are needed.

A meta-analysis to evaluate the efficacy and safety of tacrolimus and pimecrolimus was performed up to December 2008 and included 6,288 infants and children with AD.[55] Odds Ratios (ORs) for response for the tacrolimus arm versus response in control groups including vehicle, 1% hydrocortisone acetate and 1% pimecrolimus, were (4.56; 95% CI, 2.8 to 7.44), (3.92; 95% CI,: 2.96-5.2) and (1.58; 95% CI, 1.18-2.12), respectively. The effect difference between 0.03% tacrolimus and 0.1% tacrolimus ointments was not statistically significant (OR=0.9; 95% CI, 0.55-1.48). The incidence of adverse events of tacrolimus ointment or pimecrolimus cream was similar to the vehicle with burning and pruritus reported as major adverse events.

SUMMARY

Liberal use of emollients is recommended by the 2014 American Academy of Dermatology (AAD) guidelines as emollients or moisturizing agents may reduce disease severity and the need for pharmacologic intervention. In addition, these guidelines, along with the 2004 Joint Council of Allergy, Asthma and Immunology AD Practice Parameter, consider topical corticosteroids the standard of care to which other treatments are compared and are effective in a majority of patients with AD. The calcineurin inhibitors, pimecrolimus (Elidel) and tacrolimus (Protopic), are second-line agents that can be used for the treatment of acute flares of AD. In cases with disease persistence and/or frequent recurrences, topical calcineurin inhibitors are options for maintenance therapy until remission is achieved, and patients can revert back to emollient use. Unlike corticosteroids, pimecrolimus and tacrolimus are not reported to cause skin atrophy.

Rare cases of malignancies have been reported with the use of these agents, although a causal relationship has not been established. Therefore, the Food and Drug Administration (FDA) has recommended that these agents be used for the short-term and intermittent treatment of AD.

No double-blind direct comparative clinical trials exist that demonstrate clear advantages of one product over another.

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